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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Appln. of: Yamamoto et al.

Appln. No.: 10/762,028

Filed: January 20, 2004

For: CATALYTIC ASYMMETRIC
EPOXIDATION

Examiner: Bernard Dentz

Art Unit: 1625

Attorney Docket No: 7814-93

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL

Sir:

Attached is/are:

Appeal Brief
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 An additional filing fee has been calculated as shown below:

	Claims Remaining After Amendment	Minus	Highest No. Previously Paid For	Present Extra	Small Entity		Not a Small Entity		
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Total		Minus			x \$25=			x \$50=	
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Respectfully submitted,

Lisa M. Seaney, Ph.D. (Reg. No. 56,246)

12/28/05

Date



**U.S.P.S. EXPRESS MAIL "POST OFFICE TO ADDRESSEE" SERVICE
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Our Case No. 7814/93

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
Yamamoto et al.)
Serial No. 10/762,028) Examiner Bernard Dentz
Filing Date: January 20, 2004) Group Art Unit No. 1625
For: Catalytic Asymmetric Epoxidation)
)

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

By the filing of this Appeal Brief in accordance with 37 CFR § 41.37, Appellants respectfully request reconsideration by the Board of Patent Appeals and Interferences in the above-identified patent application.

Real Party in Interest

The real party in interest is The University of Chicago, having a place of business in Chicago, Illinois and Japan Science and Technology Agency having a place of business in Tokyo, Japan.

Related Appeals and Interferences

Currently, there are no pending appeals or interferences related to the present appeal.

Status of Claims

1. Claims 1-50 are present and active in the application.
2. Claims 7, 10, 39 and 40 are withdrawn from consideration
3. Claims 1-6, 8, 9, 11-38 and 41-50 have been finally rejected.
4. The rejections of claims 1-6, 8, 9, 11-38 and 41-50 are being appealed.

Status of Amendments

No amendment has been filed in this application after the August 3, 2005 final Office action.

Summary of Claimed Subject Matter

There is one (1) independent claim involved in this appeal: claim 1.

1. Independent claim 1 recites a method of performing a catalytic asymmetric oxidation that involves reacting a substrate (pages 21-23, paragraphs 88-98) with catalytic amounts of chiral bishydroxamic acid ligand (examples are disclosed in the specification at least at pages 13-20, including formula I (page 13), formula Ia' (page 15), formulae Ib' and Ic' (page 18), and formula Id' (page 20); specific examples include those at page 16, paragraph 68 and pages 25-26, paragraph 108), and a metal (e.g. page 20, paragraph 82), in the presence of an oxidation reagent (e.g. pages 20-21, paragraphs 83-87) to produce a chiral oxidation product (e.g. page 23-24, paragraphs 99-102).

Grounds of Rejection to be Reviewed on Appeal

The grounds of rejection which Appellants wish the Board to review on Appeal are the following:

1. The rejection of claims 1-6, 8, 9, 11-38 and 41-50 under 35 U.S.C. § 103(a) as being unpatentable over Hoshino *et al.* (*J. Am. Chem. Soc.* **2000**, *122*, 10452-10453).
2. The rejection of claims 1-6, 8, 9, 11-38 and 41-50 under 35 U.S.C. § 103(a) as being unpatentable over Michaelson *et al.* (*J. Am. Chem. Soc.* **1977**, *99*, 1990-1992).

Argument

Reversal of the Examiner's rejection of claims 1-6, 8, 9, 11-38 and 41-50 under 35 U.S.C. § 103(a) as being unpatentable over Hoshino and or Michaelson is respectfully requested. MPEP 2142 states that "[to] establish a *prima facie* case of obviousness...the prior art reference... must teach or suggest all the claim limitations." *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The examiner has failed to establish a *prima facie* case of obviousness for any of the claims, because each of Hoshino and Michaelson fail to teach each and every limitation of the claims as detailed below.

1. Argument with Respect to Ground of Rejection No. 1

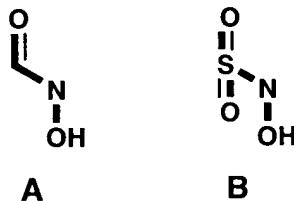
Reversal of the Examiner's rejection of claims 1-6, 8, 9, 11-38 and 41-50 under 35 U.S.C. § 103(a) as being unpatentable over Hoshino is respectfully requested.

(a) Claims 1, 3, 4, 6, 8, 9, 27, 29-32, 34, 35, 41-50.

Hoshino fails to teach, either expressly or inherently, each and every element recited in rejected independent claim 1, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected independent claim. At a minimum, the Hoshino reference fails to teach or suggest "a chiral bishydroxamic acid ligand" an element that is recited in rejected independent claim 1.

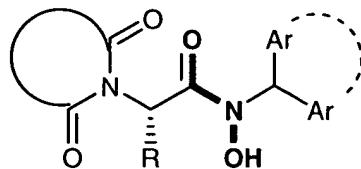
35 U.S.C. § 112, fourth paragraph, which states that “[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.” Hoshino fails to teach claim 1 and therefore also fails to teach, either expressly or inherently, each and every element recited in claims 3, 4, 6, 8, 9, 27, 29-32, 34, 35, 41-50, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected dependent claims.

The claimed invention provides methods for catalytic asymmetric oxidation involving chiral bishydroxamic acid ligands. Hydroxamic acids contain a functional group consisting of a carbonyl group (C=O) which is covalently bonded via its carbon atom to a nitrogen atom, the nitrogen atom being covalently bonded to a hydroxyl group (OH) via the oxygen atom of the hydroxyl as shown below in structure A. Alternatively, hydroxamic acids contain a function group consisting of a sulfonyl group (SO₂) which is covalently bonded via its sulfur atom to a nitrogen atom, the nitrogen atom being covalently bonded to a hydroxyl group (OH) via the oxygen atom of the hydroxyl as shown below in structure B:



The claimed invention provides for a bishydroxamic acid ligand. A bishydroxamic acid ligand contains two hydroxamic acid functional groups. For example, a bishydroxamic acid ligand may contain two functional groups of formula A, two functional groups of formula B, or alternatively a functional group of formula A and a functional group of formula B.

In contrast, Hoshino describes chiral α -amino acid-based hydroxamic acid ligands based on the following generic structure:



The Hoshino ligands contain a hydroxamic acid functional group of formula A, which is highlighted by the atoms and bonds in bold in the structure above. Each of the disclosed Hoshino ligands contains one hydroxamic acid functional group.

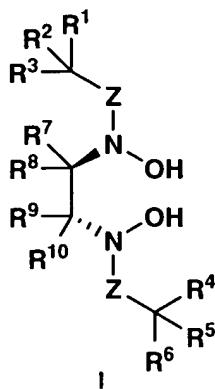
Inasmuch as Hoshino does not teach or suggest a chiral ligand with two hydroxamic acid functional groups (a chiral bishydroxamic acid ligand) as required by independent claim 1, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of Hoshino. Accordingly, reversal of this ground of rejection as to claims 1, 3, 4, 6, 8, 9, 27, 29-32, 34, 35, and 41-50 is respectfully requested.

(b) Claims 2, 11-26.

Hoshino fails to teach, either expressly or inherently, each and every element recited in rejected claim 2, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected independent claim. At a minimum, the Hoshino reference fails to teach or suggest “a chiral bishydroxamic acid ligand” with structural formula (I), an element that is recited in rejected claim 2.

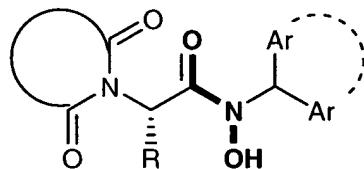
35 U.S.C. § 112, fourth paragraph, which states that “[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.” Hoshino fails to teach claim 2 and therefore also fails to teach, either expressly or inherently, each and every element recited in claims 11-26, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected dependent claims.

The claimed invention provides methods for catalytic asymmetric oxidation involving chiral bishydroxamic acid ligands of the structure (I):



where Z is -C(O)- or -S(O)₂- and R¹-R¹⁰ are defined as in claim 2. Structure (I) contains two hydroxamic acid functional groups (Z-N-OH) connected by an ethylenic linker in the manner illustrated in structure (I).

In contrast, Hoshino describes chiral α -amino acid-based hydroxamic acid ligands based on the following generic structure:



The Hoshino ligands contains one hydroxamic acid functional group, which is highlighted by the atoms and bonds in bold in the structure above. Each of the ligands disclosed by Hoshino have the generic structure illustrated by the formula above.

Inasmuch as Hoshino does not teach or suggest a chiral ligand with two hydroxamic acid functional groups arranged in the manner illustrated by structure (I) as required by claim 2, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of Hoshino. Accordingly, reversal of this ground of rejection as to claims 2, and 11-26 is respectfully requested.

(c) Claims 5 and 28.

Hoshino fails to teach, either expressly or inherently, each and every element recited in rejected claims 5 and 28, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected independent claim. At a minimum, the Hoshino reference fails

to teach or suggest (1) "a chiral bishydroxamic acid ligand"; and (2) a molybdenum (IV), molybdenum (V), or molybdenum (VI) metal, which are elements of claims 5 and 28.

The claimed invention provides methods for catalytic asymmetric oxidation involving chiral bishydroxamic acid ligands. A bishydroxamic acid ligand contains two hydroxamic acid functional groups per ligand molecule. Furthermore, the claimed invention provides methods for catalytic asymmetric oxidation involving molybdenum metal catalysts, specifically a molybdenum (IV), molybdenum (V), or molybdenum (VI) metal.

In contrast, the Hoshino ligands only provide one hydroxamic acid functional group per ligand. Hoshino describes chiral α -amino acid-based hydroxamic acid ligands based on the following generic structure:



The Hoshino ligands contain a hydroxamic acid functional group which is highlighted by the atoms and bonds in bold in the structure above. Each of the disclosed Hoshino ligands contains only one hydroxamic acid functional group. In addition, the catalytic asymmetric epoxidation method of Hoshino teaches only a vanadium metal catalyst, specifically $\text{VO}(\text{O}-i\text{-Pr})_3$. Hoshino is silent with respect to molybdenum (IV), molybdenum (V), or molybdenum (VI) metal catalysts.

Inasmuch as Hoshino does not teach or suggest a chiral ligand with two hydroxamic acid functional groups (a chiral bishydroxamic acid ligand), nor an asymmetric oxidation method with molybdenum (IV), molybdenum (V), or molybdenum (VI) metal, as required by claims 5 and 28, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of Hoshino. Accordingly, reversal of this ground of rejections as to claims 5 and 28 is respectfully requested.

(d) Claims 33 and 36.

Hoshino fails to teach, either expressly or inherently, each and every element recited in rejected claims 33 and 36, and provides no teaching or suggestion as to the

desirability of modifying the methods described therein to include each and every element of the rejected independent claim. At a minimum, the Hoshino reference fails to teach or suggest (1) "a chiral bishydroxamic acid ligand"; and (2) cumene hydroperoxide as an oxidation reagent, which are elements of claims 33 and 36.

The claimed invention provides methods for catalytic asymmetric oxidation involving chiral bishydroxamic acid ligands. A bishydroxamic acid ligand contains two hydroxamic acid functional groups per ligand molecule. Furthermore, the claimed invention provides methods for catalytic asymmetric oxidation with cumene hydroperoxide as an oxidation reagent.

In contrast, the Hoshino ligands only provide one hydroxamic acid functional group per ligand. Hoshino describes chiral α -amino acid-based hydroxamic acid ligands based on the following generic structure:



The Hoshino ligands contain a hydroxamic acid functional group which is highlighted by the atoms and bonds in bold in the structure above. Each of the disclosed Hoshino ligands contains only one hydroxamic acid functional group. In addition, the catalytic asymmetric epoxidation method of Hoshino teaches only tert-butyldihydroperoxide as the oxidation reagent. Hoshino is silent with respect to cumene hydroperoxide as an oxidation reagent.

Inasmuch as Hoshino does not teach or suggest a chiral ligand with two hydroxamic acid functional groups (a chiral bishydroxamic acid ligand), nor an asymmetric oxidation method with cumene hydroperoxide as an oxidation reagent, as required by claims 33 and 36, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of Hoshino. Accordingly, reversal of this ground of rejections as to claims 33 and 36 is respectfully requested.

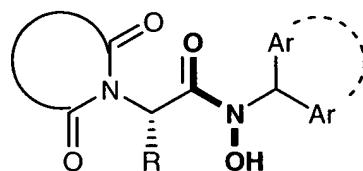
(e) Claims 37 and 38.

Hoshino fails to teach, either expressly or inherently, each and every element recited in rejected claims 37 and 38, and provides no teaching or suggestion as to the

desirability of modifying the methods described therein to include each and every element of the rejected independent claim. At a minimum, the Hoshino reference fails to teach or suggest (1) "a chiral bishydroxamic acid ligand"; and (2) hydrogen peroxide as an oxidation reagent, which are elements of claims 37 and 38.

The claimed invention provides methods for catalytic asymmetric oxidation involving chiral bishydroxamic acid ligands. A bishydroxamic acid ligand contains two hydroxamic acid functional groups per ligand molecule. Furthermore, the claimed invention provides methods for catalytic asymmetric oxidation with hydrogen peroxide as an oxidation reagent.

In contrast the Hoshino ligands only provide one hydroxamic acid functional group per ligand. Hoshino describes chiral α -amino acid-based hydroxamic acid ligands based on the following generic structure:



The Hoshino ligands contain a hydroxamic acid functional group which is highlighted by the atoms and bonds in bold in the structure above. Each of the disclosed Hoshino ligands contains only one hydroxamic acid functional group. In addition, the catalytic asymmetric epoxidation method of Hoshino teaches only tert-butylhydroperoxide as an oxidation reagent. Hoshino is silent with respect to hydrogen peroxide as an oxidation reagent.

Inasmuch as Hoshino does not teach or suggest a chiral ligand with two hydroxamic acid functional groups (a chiral bishydroxamic acid ligand), nor an asymmetric oxidation method with hydrogen peroxide as an oxidation reagent, as required by claims 37 and 38, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of Hoshino. Accordingly, reversal of this ground of rejections as to claims 37 and 38 is respectfully requested.

2. Argument with Respect to Ground of Rejection No. 2

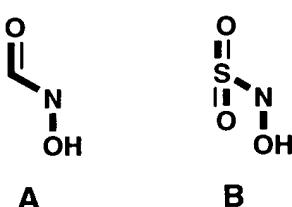
Reversal of the Examiner's rejection of claims 1-6, 8, 9, 11-38 and 41-50 under 35 U.S.C. § 103(a) as being unpatentable over Michaelson is respectfully requested.

(a) Claims 1, 3, 4, 6, 8, 9, 27, 29-36, 41-50.

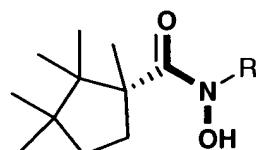
Michaelson fails to teach, either expressly or inherently, each and every element recited in rejected independent claim 1, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected independent claim. At a minimum, the Michaelson reference fails to teach or suggest “a chiral bishydroxamic acid ligand” an element that is recited in rejected independent claim 1.

35 U.S.C. § 112, fourth paragraph, which states that “[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.” Michaelson fails to teach claim 1 and therefore also fails to teach, either expressly or inherently, each and every element recited in claims 2-6, 8, 9, 11-38 and 41-50, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected claims.

The claimed invention provides methods for catalytic asymmetric oxidation involving chiral bishydroxamic acid ligands. A bishydroxamic acid ligand contains two hydroxamic acid functional groups per ligand. For example, a bishydroxamic acid ligand may contain two functional groups of formula A, two functional groups of formula B, or alternatively a functional group of formula A and a functional group of formula B. Formula A and B are shown below:



In contrast, Michaelson describes chiral hydroxamic acid ligands based on the following generic structure:



The Michaelson ligands contain a hydroxamic acid functional group of formula A, which is defined by the atoms and bonds in bold in the structure above. Each of the disclosed

Michaelson ligands contains only one hydroxamic acid functional group. The recitation in Michaelson at paragraph 2, lines 15-18, of "chiral molybdenyl bishydroxymates [O₂Mo(hydroxymate)₂]" is indicative of a transition metal (molybdenum) with two separate and distinct hydroxymate ligands. Each Michaelson hydroxymate ligand contains a single hydroxamic acid functional group.

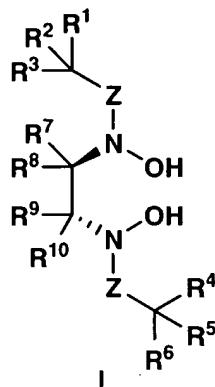
Inasmuch as Hoshino does not teach or suggest a chiral ligand with two hydroxamic acid functional groups (a chiral bishydroxyamic acid ligand) as required by independent claim 1, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of Hoshino. Accordingly, reversal of this ground of rejection as to claims 1, 3, 4, 6, 8, 9, 27, 29-36, and 41-50 is respectfully requested.

(b) Claims 2, 11-26.

Michaelson fails to teach, either expressly or inherently, each and every element recited in rejected claim 2, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected claim. At a minimum, the Michaelson reference fails to teach or suggest "a chiral bishydroxamic acid ligand" an element that is recited in rejected claim 2.

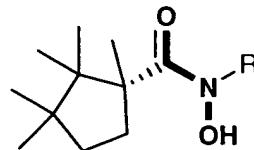
35 U.S.C. § 112, fourth paragraph, which states that "[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers." Michaelson fails to teach claim 2 and therefore also fails to teach, either expressly or inherently, each and every element recited in claims 11-26, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected claims.

The claimed invention provides methods for catalytic asymmetric oxidation involving chiral bishydroxamic acid ligands of the structure (I):



where Z is -C(O)- or -S(O)₂- and R¹-R¹⁰ are defined as in claim 2. Structure (I) contains two hydroxamic acid functional groups (Z-N-OH) connected by a two carbon linker in the manner illustrated in structure (I).

In contrast, Michaelson describes chiral hydroxamic acid ligands based on the following generic structure:



The Michaelson ligands contain one hydroxamic acid functional group, which is illustrated by the atoms and bonds in bold in the structure above. All of the ligands disclosed by Michaelson have the generic structure illustrated by the formula above.

Inasmuch as Michaelson does not teach or suggest a chiral ligand with two hydroxamic acid functional groups arranged in the manner illustrated by structure (I) as required by claim 2, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of Michaelson. Accordingly, reversal of this ground of rejection as to claims 2 and 11-26 is respectfully requested.

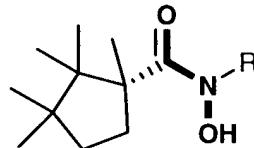
(c) Claims 5 and 28.

Michaelson fails to teach, either expressly or inherently, each and every element recited in rejected claims 5 and 28, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected independent claim. At a minimum, the Michaelson reference

fails to teach or suggest (1) "a chiral bishydroxamic acid ligand"; and (2) a molybdenum (IV), molybdenum (V), or molybdenum (VI) metal, which are elements of claims 5 and 28.

The claimed invention provides methods for catalytic asymmetric oxidation involving chiral bishydroxamic acid ligands. A bishydroxamic acid ligand contains two hydroxamic acid functional groups per ligand molecule. Furthermore, the claimed invention provides methods for catalytic asymmetric oxidation involving molybdenum metal catalysts, specifically a molybdenum (IV), molybdenum (V), or molybdenum (VI) metal.

In contrast, Michaelson describes chiral hydroxamic acid ligands based on the following generic structure:



The Michaelson ligands contain a hydroxamic acid functional group, which is defined by the atoms and bonds in bold in the structure above. Each of the disclosed Michaelson ligands contains only one hydroxamic acid functional groups. In addition, the catalytic asymmetric epoxidation method of Michaelson teaches a vanadium metal catalyst, specifically $\text{VO}(\text{acac})_2$ with at best 50% enantiomeric excess asymmetric induction (column 3, first full paragraph, lines 1-3). Furthermore, Michaelson teaches away from molybdenum metal catalysts stating at column 2, second paragraph, line 18-19, that molybdenum catalysts give poor asymmetric induction (<2%).

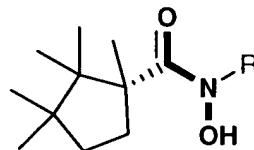
Inasmuch as Michaelson does not teach or suggest a chiral ligand with two hydroxamic acid functional groups (a chiral bishydroxamic acid ligand), nor an asymmetric oxidation method with molybdenum (IV), molybdenum (V), or molybdenum (VI) metal, as required by claims 5 and 28, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of Michaelson. Accordingly, reversal of this ground of rejections as to claims 5 and 28 is respectfully requested.

(d) Claims 37 and 38.

Michaelson fails to teach, either expressly or inherently, each and every element recited in rejected claims 37 and 38, and provides no teaching or suggestion as to the desirability of modifying the methods described therein to include each and every element of the rejected independent claim. At a minimum, the Michaelson reference fails to teach or suggest (1) "a chiral bishydroxamic acid ligand"; and (2) hydrogen peroxide as an oxidation reagent, which are elements of claims 37 and 38.

The claimed invention provides methods for catalytic asymmetric oxidation involving chiral bishydroxamic acid ligands. A bishydroxamic acid ligand contains two hydroxamic acid functional groups per ligand molecule. Furthermore, the claimed invention provides methods for catalytic asymmetric oxidation with hydrogen peroxide as an oxidation reagent.

In contrast, Michaelson describes chiral hydroxamic acid ligands based on the following generic structure:



The Michaelson ligands contain a hydroxamic acid functional group, which is defined by the atoms and bonds in bold in the structure above. Each of the Michaelson ligands contains only one hydroxamic acid functional group. In addition, the catalytic asymmetric epoxidation method of Michaelson teaches tert-butylhydroperoxide as an oxidation reagent. Michaelson is silent with respect to hydrogen peroxide as an oxidation reagent.

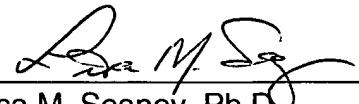
Inasmuch as Michaelson does not teach or suggest a chiral ligand with two hydroxamic acid functional groups (a chiral bishydroxamic acid ligand), nor an asymmetric oxidation method with hydrogen peroxide as an oxidation reagent, as required by claims 37 and 38, Appellants respectfully submit that the claimed invention is neither anticipated by nor would have been obvious in view of Michaelson. Accordingly, reversal of this ground of rejections as to claims 37 and 38 is respectfully requested.

Conclusion

In conclusion, Appellants respectfully submit that the two grounds of rejection raised by the Examiner have been overcome for at least the reasons set forth above. Accordingly, reversal of all grounds of rejection is respectfully requested.

Respectfully submitted,

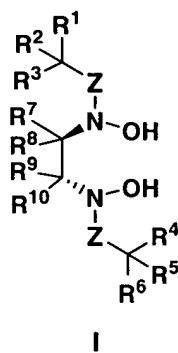
12/28/05


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Claims Appendix

1. A method of performing a catalytic asymmetric oxidation comprising:
reacting a substrate with catalytic amounts of a chiral bishydroxamic acid ligand and a metal, in the presence of an oxidation reagent, to produce a chiral oxidation product.
2. The method of claim 1, where the chiral bishydroxamic acid ligand has a structure I:



where:

R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl;

or where R^1 and R^2 , together with the atom to which they are attached, form a substituted or unsubstituted ring selected from the group consisting of cycloalkyl, heterocyclyl, or aryl;

or where R^4 and R^5 , together with the atom to which they are attached, form a substituted or unsubstituted ring selected from the group consisting of cycloalkyl, heterocyclyl, and aryl;

R^7 , R^8 , R^9 , and R^{10} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl;

or where R^7 and R^9 , together with the atoms to which they are attached, form a substituted or non-substituted ring selected from the group consisting of cycloalkyl and heterocyclyl;

$-Z-$ is selected from the group consisting of $-C(O)-$ and $-S(O)_2-$.

3. The method of claim 1, where the metal is selected from the group consisting of vanadium (IV), vanadium (V), molybdenum (IV), molybdenum (V), and molybdenum (VI).

4. The method of claim 3, where the metal is selected from the group consisting of vanadium (IV) and vanadium (V).

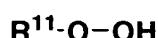
5. The method of claim 3, where the metal is selected from the group consisting of molybdenum (IV), molybdenum (V), and molybdenum (VI).

6. The method of claim 1 wherein the substrate is selected from the group consisting of sulfide, phosphine, alkene, and cyclic alkene.

7. The method of claim 6, where the substrate is selected from the group consisting of sulfide and phosphine.

8. The method of claim 6, where the substrate is selected from the group consisting of alkene and cyclic alkene.

9. The method of claim 1, where the oxidation reagent is an organic hydroperoxide with the following structure (II):



II

where, R^{11} is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl.

10. The method of claim 1 wherein the chiral oxidation product has a structure

III:



III

where,

Y is selected from the group consisting of sulfides and phosphines.

11. The method of claim 2, where the substrate is an alkene or cyclic alkene.

12. The method of claim 2, where R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, and alkylamino.

13. The method of claim 2, where R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from the group consisting of cycloalkyl and heterocyclyl.

14. The method of claim 2, where R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are each independently selected from the group consisting of aryl, arylalkyl, heteroaryl, and halogen.

15. The method of claim 2, where:

R^1 and R^2 , together with the atom to which they are attached, form a substituted or unsubstituted ring;

R^4 and R^5 , together with the atom to which they are attached, form a substituted or unsubstituted ring; and

the ring formed by R^1 and R^2 is identical to the ring formed by R^4 and R^5 .

16. The method of claim 2, where R^7 , R^8 , R^9 , and R^{10} are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, and alkylamino.

17. The method of claim 2, where R^7 , R^8 , R^9 , and R^{10} are each independently selected from the group consisting of cycloalkyl and heterocyclyl.

18. The method of claim 2, where R^7 , R^8 , R^9 , and R^{10} are each independently selected from the group consisting of aryl, arylalkyl, and heteroaryl.

19. The method of claim 2, where R^7 and R^9 , together with the atoms to which they are attached, form a ring.

20. The method of claim 19, where R^8 and R^{10} are identical.

21. The method of claim 17, where R^7 and R^9 , together with the atoms to which they are attached, form a ring.

22. The method of claim 21, where R^8 and R^{10} are identical.

23. The method of claim 2, where:

R^1 and R^2 are aryl groups;

R^3 is hydrogen;

R^4 and R^5 are aryl groups; and

R^6 is hydrogen.

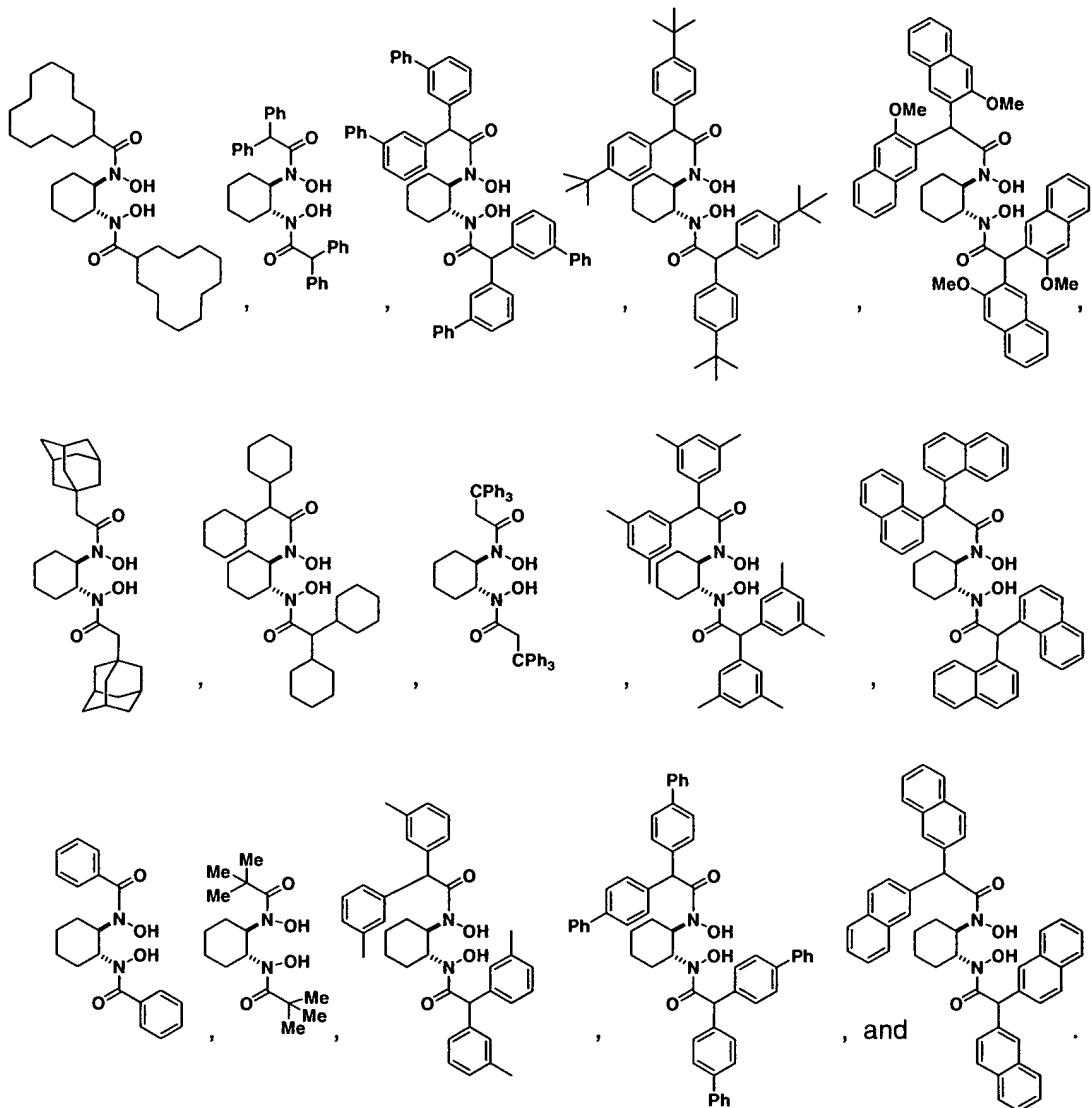
24. The method of claim 23, where:

R^1 and R^2 are identical; and

R^4 and R^5 are identical.

25. The method of claim 24, where R¹, R², R⁴, and R⁵ are identical.

26. The method of claim 2, where the chiral bishydroxamic acid ligand (I) is selected from the group consisting of:



27. The method of claim 6, where the metal is selected from the group consisting of vanadium (IV) and vanadium (V).

28. The method of claim 8, where the metal is selected from the group consisting of molybdenum (IV), molybdenum (V), and molybdenum (VI).

29. The method of claim 3, where the metal is selected from the group consisting of $\text{VO}(\text{OPr})_3$, $\text{VO}(\text{acac})_2$, $\text{VO}(\text{OEt})_3$, and $\text{MoO}_2(\text{acac})_2$.

30. The method of claim 8, where the metal is selected from the group consisting of $\text{VO}(\text{OPr})_3$, $\text{VO}(\text{acac})_2$, $\text{VO}(\text{OEt})_3$, and $\text{MoO}_2(\text{acac})_2$.

31. The method of claim 9, where the organic hydroperoxide is selected from the group consisting of tert-butyl hydroperoxide and cumene hydroperoxide.

32. The method of claim 9, where the organic hydroperoxide is tert-butyl hydroperoxide.

33. The method of claim 9, where the organic hydroperoxide is cumene hydroperoxide.

34. The method of claim 8, where the oxidation reagent is selected from the group consisting of tert-butyl hydroperoxide and cumene hydroperoxide.

35. The method of claim 8, where the oxidation reagent is tert-butyl hydroperoxide.

36. The method of claim 8, where the oxidation reagent is cumene hydroperoxide.

37. The method of claim 1, where the oxidation reagent is hydrogen peroxide.

38. The method of claim 8, where the oxidation reagent is hydrogen peroxide.

39. A method of preparing a chiral bishydroxamic acid ligand comprising:

condensing an optically active 1,2-diammonium tartarate with p-anisaldehyde to provide a di-imine;

oxidizing the di-imine to produce a dioxaziridine;

hydrolyzing the dioxadiaziridine to generate a dihydroxylamine hydrochloride;

silylating the dihydroxylamine hydrochloride to provide a silyl protected dihydroxylamine;

condensing the silyl protected dihydroxylamine with an acid chloride to produce the chiral bishydroxamic acid ligand.

40. The method of claim 39, where the chiral bishydroxamic acid ligand is prepared by a method comprising:

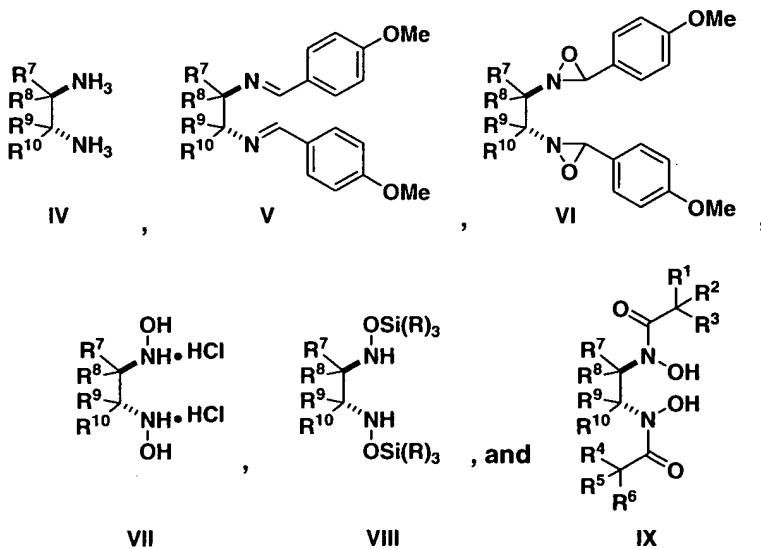
condensing an optically active 1,2-diammonium tartarate (IV) with p-anisaldehyde to provide a di-imine (V);

oxidizing the di-imine (V) to produce a dioxadiazine (VI);

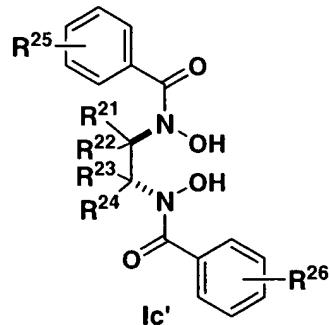
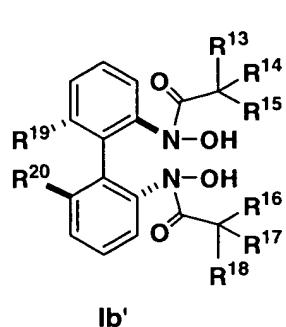
hydrolyzing the dioxadiazine (VI) to generate a dihydroxylamine hydrochloride (VII);

silylating the dihydroxylamine hydrochloride (VII) to provide a silyl protected dihydroxylamine (VIII);

condensing the silyl protected dihydroxylamine with an acid chloride to produce the bishydroxamic acid (IX).



41. The method of claim 1, where the chiral bishydroxamic acid ligand (I) is selected from the following formulae:



where:

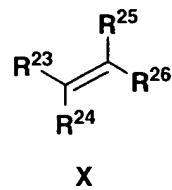
R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R¹⁸ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl;

R¹⁹ and R²⁰ are each independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl;

R²¹, R²², R²³, and R²⁴ are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl;

R²⁵ and R²⁶ are each independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl.

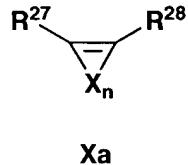
42. The method of claim 8, where the alkene is of the formula (X):



where:

R^{23} , R^{24} , R^{25} , and R^{26} are each independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, heteroaryl, and arylalkyl.

43. The method of claim 8, where the alkene is a cyclic alkene of the formula (Xa):



where:

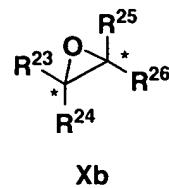
R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, aralkyl, heteroaryl, halogen, and alkene;

n is 1, 2, 3, 4, 5, 6, or 6;

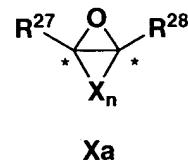
each X is independently selected from the group consisting of $-\text{CR}'\text{R}''$, $-\text{NR}'-$, and $-\text{O}-$;

R' and R'' are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkoxy, alkylamino, heterocyclyl, aryl, aralkyl, heteroaryl, and halogen.

44. The method of claim 42, where the chiral oxidation product is of the formula (Xb):



45. The method of claim 43, where the chiral oxidation product is of the formula (Xc):



46. The method of claim 1, where the reacting step is carried out in a solvent.

47. The method of claim 46, where the reacting step is carried out in a solvent selected from the group consisting of methylene chloride, toluene, chloroform, and ethyl acetate.

48. The method of claim 1, where the reacting step is carried out at a temperature of about -20 to about 25 °C.

49. The method of claim 1, where the reaction is carried out with about 0.001 to about 0.1 equivalents of the chiral bishydroxamic acid ligand (I).

50. The method of claim 1, where the reaction is carried out with about 0.005 to about 0.05 equivalents of metal.

Evidence Appendix

Exhibit I contains a copy of Hoshino *et al.* (*J. Am Chem. Soc.* **2000**, *122*, 10452-10453).

Exhibit II contains a copy of Michaelson *et al.* (*J. Am Chem. Soc.* **1977**, *99*, 1990-1992).

The documents contained in Exhibits I and II were originally entered by the Examiner in the February 25, 2005 Office Action. Scans of these documents are contained in the PAIR system's Image File Wrapper for this application under the Document Description heading "NPL Documents" entered 2/25/05.

EXHIBIT I

Novel α -Amino Acid-Based Hydroxamic Acid Ligands for Vanadium-Catalyzed Asymmetric Epoxidation of Allylic Alcohols

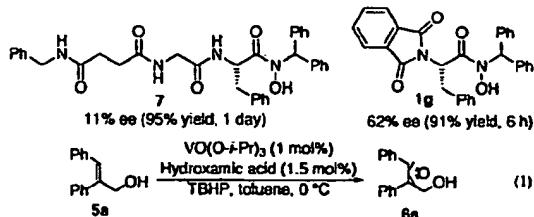
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Received July 17, 2000

The development of novel effective chiral catalysts for enantioselective synthesis is a current topic of interest in synthetic organic chemistry.¹ Hydroxamic acids are good ligands for metal ions and are used as indicators for detecting metal ions.² In 1977, Sharpless and co-workers reported that hydroxamic acids are very resistant to oxidation and seem to bind well to molybdenyl and vanadium ions. They performed the asymmetric epoxidation of allylic alcohols in the presence of $\text{VO}(\text{acac})_3$ and chiral hydroxamic acids.^{3,4} However, catalysts of this type were not developed to a useful level, due to ligand deceleration along with dynamic ligand exchange processes in this system.⁴ We recently described the vanadium-catalyzed asymmetric epoxidation of allylic alcohols using chiral binaphthyl-modified hydroxamic acids.⁵ Our results suggested that several characteristics of the chiral vanadium complex play an important role in increasing the rate and enantioselectivity, i.e., the starting oxidation state of vanadium, the coordination ability of hydroxamic acids, and π -interaction or steric repulsion between the metal-binding site and oxidant. To improve this catalyst system, we planned to use combinatorial and related strategies⁶ to identify effective vanadium-based catalysts for asymmetric epoxidation. For this purpose, our hydroxamic acid-bearing binaphthyl group can be reconstructed to novel α -amino acid-based hydroxamic acids suitable for the synthesis of a ligand library (Scheme 1). We report here that chiral α -amino acid-based hydroxamic acid ligands with a very simple structure are efficient catalysts for the asymmetric epoxidation of allylic alcohols.

In a preliminary experiment, hydroxamic acid **1g** derived from phenylalanine gave better results than the peptide hydroxamic acid **7** in the asymmetric epoxidation of (*E*)-2,3-diphenyl-2-propen-1-ol (eq 1).⁷ This reaction was also conducted in a water-



free atmosphere, and a family of hydroxamic acids of this type were easily prepared from commercially available materials: a free α -amino acid was treated with appropriate carboxylic acid anhydride in DMF at 100 °C to give *N*-protected amino acid,

(1) For a recent review, see: *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999.

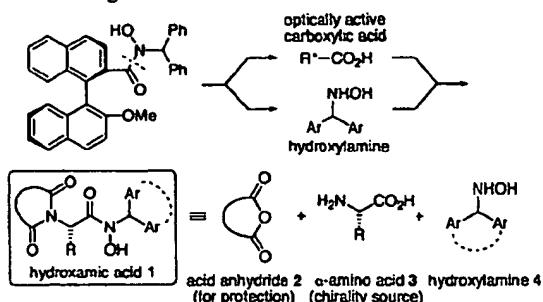
(2) Yale, H. L. *Chem. Rev.* 1943, 33, 209.

(3) (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* 1977, 99, 1990. (b) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* 1979, 12, 63. (c) Sharpless, K. B. *CHEMTECH* 1985, 15, 692. (d) Bernisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* 1995, 34, 1059.

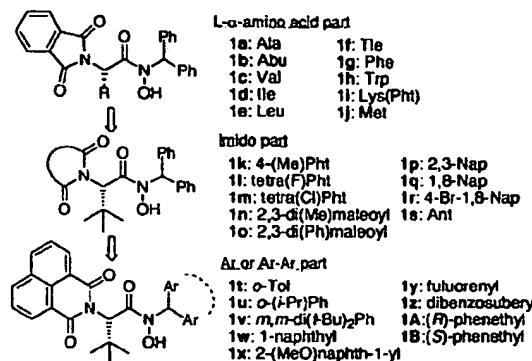
(4) For recent reports on chiral vanadium-catalyzed epoxidation, see: (a) Bolm, C.; Luong, T. K. K.; Hamm, K. *Chem. Ber./Recl.* 1997, 130, 887. (b) Bolm, C.; Kühn, T. *Synlett* 2000, 899.

(5) (a) Murase, N.; Hoshino, Y.; Oishi, M.; Yamamoto, H. *J. Org. Chem.* 1999, 64, 338. (b) Hoshino, Y.; Murase, N.; Oishi, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* In press.

Scheme 1. Design of an α -Amino Acid-Based Hydroxamic Acids as a Ligand



Scheme 2. Iterative Positional Optimization Approach



which was transformed to acid chloride in the usual manner, and then treated with hydroxylamine to give the desired hydroxamic acid.⁸ These features prompted us to optimize α -amino acid-based hydroxamic acids as ligands in the asymmetric epoxidation of allylic alcohols by using an iterative positional optimization approach, which involves screening one component of a ligand structure for selectivity, while holding the other units constant.⁶

We developed a family of chiral hydroxamic acid ligands with a general structure of **1**, which consists of α -amino acid **3**, N^{α} -protecting group **2**, and hydroxylamine **4** (Scheme 2).⁹ The enantioselectivities of epoxy alcohol **6a** obtained from asymmetric epoxidation in the presence of $\text{VO}(\text{O}-i\text{-Pr})_3$ (1 mol %) and ligand **1** (1.5 mol %) at 0 °C for 6 h in toluene were investigated, and these results are shown in Figure 1.⁷ In the first step, the source of chirality for ligand **1**, the amino acid moiety, was optimized. The selectivity of the product gradually increased with an increase in the steric hindrance of the side chain of the amino acid (from

(6) (a) Kuntz K. W.; Snapper, M. L.; Hoveyda, A. H. *Curr. Opin. Chem. Biol.* 1999, 3, 313. (b) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. In *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, 1389 and references therein.

(7) A representative procedure for the asymmetric epoxidation of **5a** in the presence of $\text{VO}(\text{O}-i\text{-Pr})_3$ and hydroxamic acid **1g**: the hydroxamic acid ligand **1g** (30.0 mg, 0.063 mmol) was dissolved in toluene (4.2 mL). 10 μL of $\text{VO}(\text{O}-i\text{-Pr})_3$ (0.042 mmol) was added, and the mixture was stirred for 1 h at room temperature while it turned light brown. The resulting solution was cooled to 0 °C, 78% *tert*-butylhydroperoxide (TBHP) (0.73 mL, 6.3 mmol) and allyl alcohol **5a** (883 mg, 4.2 mmol) were added, and the mixture was stirred for 6 h at 0 °C. Saturated aqueous solution of Na_2SO_3 was added, and the mixture was stirred for 1 h at 0 °C, allowed to warm to room temperature, extracted with ether, and dried over Na_2SO_4 . The organic phase was concentrated under reduced pressure, and the residue was purified by column chromatography (ethyl acetate/hexane = 1:2) to give the epoxy alcohol **6a** (865 mg, 91%; 62% ee).

(8) See the Supporting Information for detailed experimental procedures.

(9) The abbreviations for the components of hydroxamic acids are explained in the Supporting Information.

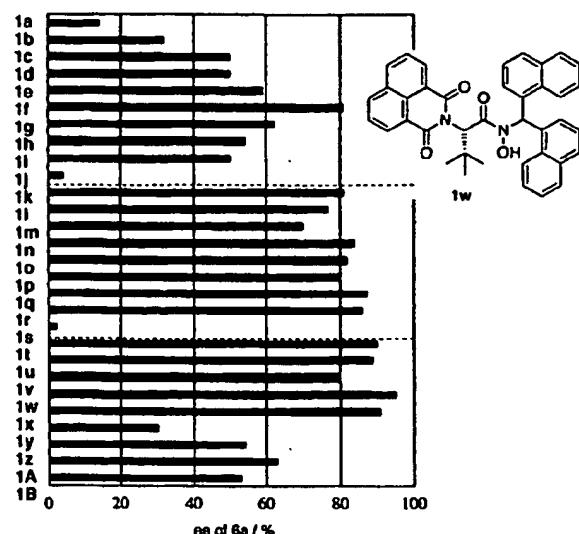
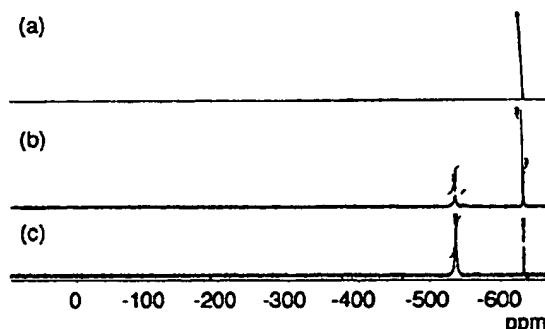


Figure 1. Enantioselectivities of epoxy alcohol 6a.

Figure 2. ^{51}V NMR spectra in benzene- d_6 at room temperature (VOCl_3 , 0 ppm): (a) $\text{VO(O-}i\text{-Pr)}_3$, (b) $\text{VO(O-}i\text{-Pr)}_3$ and ligand 1w (molar ratio, 1:1), and (c) $\text{VO(O-}i\text{-Pr)}_3$ and ligand 1w (molar ratio, 1:1.5).

1a to 1f), and the best result in this case was achieved using *tert*-leucine-derived hydroxamic acid 1f. In the second step, the imido group was examined and optimized to 1,8-naphthalenedicarbonyl-protected hydroxamic acid 1q (87% ee). Finally, the aryl groups near the metal-coordination site were changed. Interestingly, ligands that connected the phenyl groups gave low ee (1y, z). The best result was obtained using *N*-bis(1-naphthyl)methyl-substituted hydroxamic acid 1w (entry 1, Table 1).¹⁰ This reaction system was also tested to be conducted under an atmosphere of dry argon, and gave almost the same result (entry 2).

Some mono- or disubstituted allylic alcohols were enantioselectively epoxidized in good to high selectivity in the presence of optimized ligand 1w (Table 1). Disubstituted allylic alcohols, except the 3-cis-substituted one, were epoxidized with excellent enantioselectivities and yields (6a–c). Even though 1w was optimized for a particular substrate, it was an effective catalyst for a range of disubstituted allylic alcohols, and gave products with moderate-to-high enantioselectivity and yield (6d,e). The reactions of monosubstituted allylic alcohols in asymmetric epoxidation require a longer reaction time and give the corresponding epoxy alcohols with 76–87% ee.

The best catalyst identified by the above screening, 1w, was also effective as a low-loading catalyst (0.1 mol %), but with a slight loss of selectivity (entry 3). This constitutes the first example of high enantioselectivity in vanadium-catalyzed asymmetric

(10) This ligand is a colorless crystal that is suitable for X-ray crystal structure analysis. The results of this analysis are shown in the Supporting Information.

Table 1. The Asymmetric Epoxidation of Various Allylic Alcohols in the Presence of $\text{VO(O-}i\text{-Pr)}_3$ (1 mol %) and Hydroxamic Acid 1w (1.5 mol %)^a

entry	epoxy alcohol 6	time (h)	yield (%) ^b	ee (%) ^c
1				
2 ^g		6	93	96
3 ^h		15	99	86
4 ⁱ		6	98	91
5		6	97	95
6		5	82	93 ^d
7		6	95	81 ^d
8		3	97	78 ^d
9		70	94	83 ^d
10		80	58 ^e	87
11		1 week	71 ^f	76
12		24	80	82 ^d

^a All reactions were carried out at 0 °C in the presence of 1.5 equiv of *tert*-butylhydroperoxide and 1 mol % of vanadium catalyst prepared *in situ* by mixing $\text{VO(O-}i\text{-Pr)}_3$ and ligand 1w (V/ligand 1:1.5) unless otherwise noted. ^b Isolated yield by column chromatography. ^c Determined by HPLC analysis with a chiral column (Chiral OD-H) unless otherwise noted. ^d Determined by GLC analysis with a chiral stationary phase column (β -TA). ^e The aldehyde was obtained in 9% yield as a byproduct. The allyl alcohol was recovered in 8% yield. ^f The allyl alcohol was recovered in 21% yield. ^g The reaction was conducted under an atmosphere of dry argon. ^h 0.1 mol % of $\text{VO(O-}i\text{-Pr)}_3$ and 0.15 mol % of 1w were used. ⁱ 1.1 mol % of 1w was used.

epoxidation with high reactivity. To understand the structure of the catalyst, a ^{51}V NMR experiment was performed (Figure 2). When hydroxamic acid 1w in benzene- d_6 was treated with an equimolar amount of $\text{VO(O-}i\text{-Pr)}_3$ at room temperature, two peaks were observed at -537 and -633 ppm, as shown in Figure 2b. The peak at -537 ppm increased when the amount of 1w was increased (the ratio of integration of these peaks is 95:5 (-537 ppm/-633 ppm) with the addition of 1.5 equiv of ligand, Figure 2c). This peak can be assigned to $\text{VO(O-}i\text{-Pr)}_2(\text{L})$ (L = hydroxamate of 1w). This observation suggests that 1:1 complexation of vanadium and ligand was effective, and this would positively affect the enantioselectivity.

These results show that chiral amino acid-based hydroxamic acids identified from libraries can be effective asymmetric catalysts for the epoxidation of allylic alcohols, especially disubstituted allylic alcohols. The mild reaction conditions, e.g., reasonable temperature (0 °C), low degree of catalytic loading (1 mol % of vanadium), and halogen-free solvent (toluene), extend the scope of this process. Experiments are in progress to identify effective asymmetric catalysts for other important reactions using this positional optimization strategy.

Acknowledgment. The authors thank Dr. Masataka Oishi for his useful suggestions. Y.H. acknowledges a JSPS Fellowship for Japanese Junior Scientists.

Supporting Information Available: Experimental details for preparing hydroxamic acid ligand 1 and the asymmetric epoxidation of allylic alcohol 5, and spectroscopic data for 1 (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

EXHIBIT II

Collect. Czech. Chem. Commun., 32, 3897 (1987).

(10) 3a: ν_{max}^{NMR} cm⁻¹: 1595, 1275 (MeCOCHCOMe); 930, 810 (O=Mo=O);¹¹ NMR (in CDCl₃-CD₃OD (1 drop)-Me₂Si): δ 1.05 (3 H, d, J = 6.5 Hz, NCH-CH₂), 2.03 (6 H, s, CH₂COCHCOCH₂), 2.83 (8 H, s, N(CH₃)₂), 2.8-3.4 (2 H, m, OCH-CHN), 5.3-5.5 (1 H, broad s, COCHCO), 7.32 (5 H, s, C₆H₅). Anal. Calcd for C₁₉H₂₂O₅Mo: C, 47.42; H, 5.72; N, 3.46. Found C, 47.44; H, 5.74; N, 3.62. 3b: IR ν_{max}^{NMR} cm⁻¹: 1595, 1280(MeCOCHCOMe); 930, 810 (O=Mo=O);¹¹ NMR (in CDCl₃-CD₃OD (1 drop)-Me₂Si): δ 0.98 (3 H, d, J = 7 Hz, NCH-CH₂), 1.23 (3 H, l, J = 7 Hz, NCH₂CH₂), 2.01 (8 H, s, CH₂COCHCOCH₂), 2.68 (3 H, s, CH₃), 4.0-4.5 (4 H, broad m, OCH-CHN and NCH₂CH₃), 5.2-5.8 (1 H, broad s, COCHCO), 7.25 (5 H, s, C₆H₅).

(11) P. C. H. Mitchell, Q. Rev. (Chem. Soc.), 20, 103 (1966).

(12) When the reaction temperature is lowered, the optical yield of 2 is clearly increased with a remarkable delay of the epoxidation speed. This tendency, which is frequently observed in usual asymmetric synthesis, can be visualized in the following data for the epoxidation of 1b in the presence of 3a: reaction temperature, reaction time, chemical yield, optical yield: 30-35 °C, 8 days, 43%, 15%; 40-45 °C, 60 h, 39%, 10%; 70-75 °C, 20 h, 47%, 4.5%. Therefore, the reaction temperature was kept in a range of 40-45 °C to complete the epoxidation within a moderate period.

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Received July 6, 1976

Chiral Hydroxamic Acids as Ligands in the Vanadium Catalyzed Asymmetric Epoxidation of Allylic Alcohols by *tert*-Butyl Hydroperoxide

Sir:

In spite of great current interest in asymmetric synthesis¹ little has been achieved in the area of asymmetric oxidations. By contrast asymmetric reductions have been quite successful, and, in the case of hydrogenation of certain olefins,² remarkably so. Of all organic oxidations, the epoxidation of olefins would be the most useful to accomplish in an asymmetric

manner. The best induction to date with simple olefins is 10% enantiomeric excess (ee) realized using percamphoric acid.^{3,18} Recently Wynberg and co-workers have reported substantial (25%) inductions in the epoxidation of α,β -unsaturated ketones by alkaline hydrogen peroxide employing chiral phase transfer agents.⁴ We felt that the transition metal catalyzed epoxidations of olefins by alkyl hydroperoxides^{5,15d} offered a special opportunity to achieve asymmetric epoxidations. Therefore we have, for the past few years,^{9a} been investigating the effects of chiral ligands on these systems and report here our initial successes.

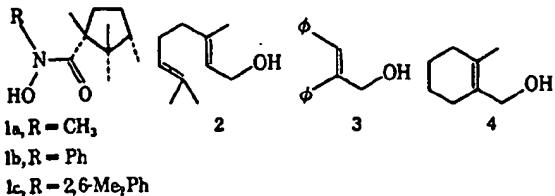
From our earlier results on the vanadium and molybdenum catalyzed epoxidations of allylic alcohols,^{5b,5c} we had good evidence that the alcohol function was coordinated to the metal during the oxygen atom transfer step. This attachment of the allylic alcohol substrate to the metal was expected to enhance any asymmetric selection process. All that seemed necessary was to find a chiral ligand which was stable to the conditions and did not block coordination sites essential to the epoxidation process. We first investigated chiral β -diketone⁶ complexes of vanadium and molybdenum; these gave poor results and we have since found that β -diketones are rapidly destroyed under the conditions of these oxidations.⁷ After trying a variety of other chiral ligands, hydroxamic acids were found to be especially attractive.^{9a} They are very resistant to oxidation and seem to bind well to molybdenum and vanadium. Well characterized, chiral molybdenyl bishydroxymates [O₂Mo(hydroxymate)₂] were easily prepared from chiral hydroxamic acids such as 1a.^{9a} However, these molybdenum complexes⁸ have so far given poor (<2%) asymmetric inductions. On the other hand, although we have not yet managed to prepare a characterizable chiral hydroxymate complex of vanadium,^{9b} asymmetric epoxidations with *in situ* generated vanadium hydroxymates have been encouraging. The results using vanadium catalysis with three related chiral hydroxamic acids (1a-1c)¹⁰ and three allylic alcohols (geraniol (2), *E*- α -phen-

Table I. Asymmetric Epoxidations of Allylic Alcohols^a

Hydroxamic acid (equiv) ^b	Allylic alcohol	°C	% ee ^c	% conversion ^d
1 1a (5)	2	-78 → 25	17	83
2 1a (3)	3	-78 → 25	10	100
3 1a (5)	3	-78 → 25	21	80
4 1a (10)	3	-78 → 25	18	22
5 1b (4)	2	-78 → 25	19	100
6 1b (4)	2	25	17.5	100
7 1b (5)	2	25	30	86
8 1b (5)	2	-78	—	0
9 1b (7)	2	-78 → 25	10	10
10 1b (1)	3	-78 → 25	<8	100
11 1b (2)	3	-78 → 25	8	100
12 1b (3)	3	-78 → 25	22.5	100
13 1b (5)	3	-78 → 25	50	30
14 1b (5)	3	25	40	84
15 1b (5)	4	25	40	87
16 1b (5)	4	-10	44	75
17 1c (3)	2	0	5	70
18 1c (4)	2	0	19	55
19 1c (5)	2	0	—	0

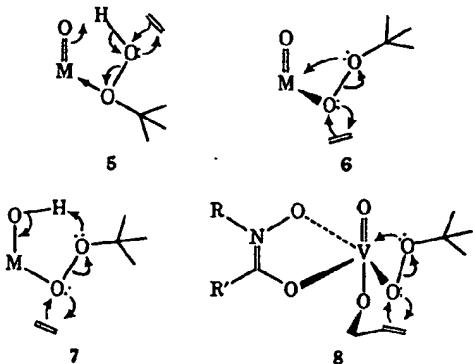
^a All reactions were performed with 1 mmol of allylic alcohol and 2.5 mg (1%) of VO(acac)₂ catalyst in 20 mL of toluene under a nitrogen atmosphere. When the appropriate amount of hydroxamic acid was added to these solutions they immediately turned from green to reddish brown in color. Stirring was continued at room temperature for 15 min then, after cooling, 2 equiv of *tert*-butyl hydroperoxide (90+, Lucidol) was added dropwise. During addition of the hydroperoxide the solution turned ruby red and this color persisted even after warming to room temperature. Reactions were monitored by TLC and acetylation was accomplished *in situ* by addition of pyridine and acetic anhydride. Acetylation was allowed to proceed for 2 h at room temperature and workup (see ref 5b) afforded the crude epoxyacetates which were purified by PLC and/or microdistillation. ^b The figure in parentheses refers to the equivalents of hydroxamic acid added based on the amount of VO(acac)₂ catalyst. ^c The enantiomeric excess (ee) was determined by ¹H NMR using Eu-OPTISHIFT II [Eu(hfbc)₂] chiral shift reagent on the epoxyacetates (see ref 13 for estimated rotations of the three epoxyacetates). ^d The percent of epoxy alcohol product plus the percent of unreacted allylic alcohol equals 100%. In cases of 100% conversion the isolated yields of epoxy acetates ranged from 70 to 90%.

ylcinnamyl alcohol (3),¹¹ 1-hydroxymethyl-2-methylcyclohexene (4)¹² are shown in Table I.¹³



The best induction (50% ee) was attained in epoxidation of α -phenylcinnamyl alcohol 3 employing *N*-phenylcamphor-10-hydroxamic acid (1b) as the chiral ligand (Table I, entry 13). Trends relating to reaction temperature and the amount of chiral ligand used can be gleaned from Table I. In general, lower temperatures lead to higher inductions (e.g., Table I entries 13 and 14); however, this positive effect is counterbalanced by a tendency toward incomplete conversion as the temperature is lowered. As a rule the optimum inductions were realized when the ratio of hydroxamic acid to $\text{VO}(\text{acac})_2$ catalyst was about 5:1. Although not mentioned in Table I, it was found that cumene-hydroperoxide gave substantially poorer inductions than *tert*-butyl hydroperoxide in three different cases where the two were compared. In order to explain such effects one must know the mechanism of these reactions.

We have recently¹⁴ suggested a new possibility for the mechanism of these epoxidations. The previous¹⁵ mechanisms proposed by three different groups, although different in detail, all favor transition states resembling 5 in the scheme; these



mechanisms accomplish activation of the hydroperoxide by coordination to the metal of the oxygen proximal to the alkyl group. In contrast we favor coordination of the hydroperoxide by the oxygen distal to the alkyl group and subsequent oxygen transfer by one or both of the two paths depicted in 6 and 7 of the scheme. The arguments supporting transition states resembling 6 and 7 over those such as 5 are discussed elsewhere;¹⁴ however, an obvious difficulty for the type 5 mechanism is rationalization of the great rate accelerations observed in epoxidations of allylic alcohols with these systems. It is geometrically impossible to coordinate the hydroxyl group of an allylic alcohol to the metal and at the same time allow the olefinic bond to take up the direction of approach to the peroxidic oxygen required in 5. On the other hand, mechanisms such as 6 and 7 easily accommodate coordination of the allylic alcohol to the metal. For the present reactions with vanadium in the presence of hydroxamic acid ligands we very tentatively suggest a mechanism whose general features are shown in 8 of the scheme.¹⁶

The results reported here are obviously of a preliminary nature. Much work remains to be done, especially with vari-

ation of the chiral ligands. Also underway are investigations on the effects of chiral hydroxamic acids on other transition metal catalyzed processes.

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- (8) The use of achiral molybdenum(VI) hydroxamates as epoxidation catalysts has been reported by F. Trifari, P. Forzatti, S. Pretili, and I. Pasquon, *J. Less-Common Met.*, **38**, 319 (1974).
- (9) (a) The first chiral molybdenyl bishydroxamate was prepared from 1a in 1973 (R. C. Michaelson, Ph.D. Thesis, Massachusetts Institute of Technology, Jan. 1976). (b) It is our impression, based on limited experience, that vanadium hydroxamate complexes are considerably more labile than their molybdenum analogues. For example, the vanadium complexes do not appear to tolerate silica gel chromatography.
- (10) All three hydroxamic acids were prepared by acylation of the corresponding hydroxyl amine with camphor-10-chloride. Different procedures were employed. In the case of 1b 2 equiv of phenylhydroxylamine were added to a solution of camphor-10-chloride in acetonitrile. We have found this method (developed in our laboratory by Dr. Steven Current) to be very effective for preparing a variety of substituted hydroxamic acids. Hydroxamic acids 1a and 1c were prepared by reaction of the lithium salt of the hydroxyl amine with camphor-10-chloride in THF.
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- (13) All three allylic alcohols gave dextrorotatory epoxycetates with each of the three (1a, 1b, 1c) chiral hydroxamic acids. Based on the chiral shift reagent determinations (Table I) and the measured rotations of the enriched epoxycetate products, the approximate absolute rotations for the epoxycetates derived from allylic alcohols 2, 3, and 4, respectively, are calculated to be $[\alpha]^{20}_D$ 7.8° (c 2.0, acetone), $[\alpha]^{30}_D$ 44° (c 2.7, CCl_4), and $[\alpha]^{30}_D$ 34° (c 2.8, acetone).
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- (16) The hypothesis that a vanadium monohydroxamate complex (e.g., 8) is the effective chiral catalyst seems reasonable in light of our experience with molybdenum bishydroxymates. Furthermore, even the most rudimentary mechanistic considerations would seem to require at least two available cis-coordination sites for these epoxidations to proceed; it is difficult to see how this criterion could be fulfilled by a vanadium(V) species bearing more than one hydroxamic acid ligand. It might be argued that these considerations are difficult to reconcile with the fact (see Table I) that optimum asymmetric inductions are realized with rather high (~ 5) hydroxamic acid/vanadium ratios. However, we feel that this phenomenon is likely due to the importance of minimizing the presence of vanadium species bearing no hydroxamate ligands (such species would produce racemic epoxide) while at the same time maintaining a population of the active monohydroxamate species which is sufficient to sustain a reasonable rate of catalysis. Although a vanadium(IV) catalyst is added we and others (see ref 15b) assume that it is rapidly oxidized to a vanadium(V) species by the *tert*-butyl hydroperoxide. In the molybdenum catalyzed epoxidations it has been proven that a molybdenum(VI) species is rapidly formed regardless of the oxidation state of the molybdenum compound originally added (R. A. Sheldon, *Rec. Trav. Chim. Pays-Bas*, **92**, 367 (1973)).
- (17) Yamada, Meshiko, and Terashima *J. Am. Chem. Soc.*, preceding paper in this issue, have found that N-alkyl ephedrine complexes of molybdenum(VI) effect asymmetric epoxidation of allylic alcohols. For geraniol, they have nicely correlated the 2,3-epoxide produced with ($\text{R}_1\text{R}_2\text{R}_3\text{R}_4$)- $\text{H}_2\text{C}=\text{CH}-\text{CH}_2\text{OH}$, thereby establishing the absolute configuration of their (+)-2,3-epoxy-

geraniol as 2(R), 3(R). We have found that the (+)-2,3-epoxygeraniol acetate produced in our system (entry 7, Table I) gives (−)-2,3-epoxygeraniol upon hydrolysis (K_2CO_3 , MeOH). Thus, in the case of geraniol, the two systems selectively form opposite epoxide enantiomers.

(18) Sizeable asymmetric inductions (ca. 50% ee) have been attained in the formation of oxaziridines by the reaction of chiral peracids with imines (see J. Bjørge, D. R. Boyd, R. M. Campbell, N. J. Thompson, and W. B. Jennings, *J. Chem. Soc., Perkin Trans. 2*, 608 (1976), and references cited therein).

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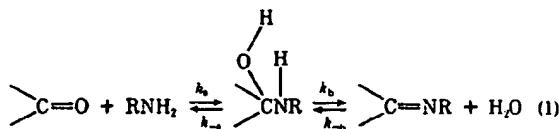
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Rate of Carbinolamine Formation between Pyridoxal 5'-Phosphate and Alanine¹

Sir:

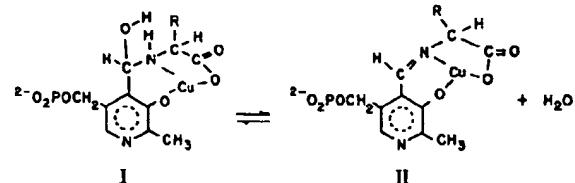
In Schiff base formation reactions between amines and carbonyl compounds a two-step mechanism involving an intermediate carbinolamine is often observed.²⁻⁴ However, in



the reactions of the physiologically important pyridoxal 5'-phosphate (PLP), 3-hydroxypyridine-4-carboxaldehyde⁵ or salicylaldehyde,⁶ carbinolamine does not form in readily detectable amounts. The same rate equation, which is first order in each of aldehyde and amine, describes both the disappearance of aldehyde and the formation of aldimine. In two limiting cases which could account for this behavior either a low pre-equilibrium concentration of carbinolamine is formed with dehydration being rate limiting, or carbinolamine formation is rate limiting with dehydration being fast. Arguments in favor of the latter mechanism have been presented.^{5,7} Alternatively, an intermediate steady state situation could exist. By trapping the carbinolamine formed during the reaction of PLP and ala with Cu(II) we have been able to determine both the stability of the Cu(II)-carbinolamine complex and the rate law for its formation. Both Cu(II) independent and dependent pathways were found. A comparison of the values of the rate constants found for the former set of reactions with those found for the formation of (*N*-pyridoxylidene 5'-phosphate)alaninate in the absence of Cu(II) shows unequivocally that carbinolamine formation in this system is considerably faster than dehydration.

Intermediates having a lower absorbance in the near-UV than either reactants or products have been observed in the hydrolysis of bis(*N*-salicylideneethylamine)copper(II) in borax

buffers at pH 8.5,⁸ and during the reaction of PLP with glutamate in the presence of Cu(II).⁹ These intermediates have been attributed to Cu(II) carbinolamine complexes. We have found that under certain conditions on mixing PLP with copper(II)-alanine solution⁵ the absorbance bands of PLP decrease in intensity owing to a reaction which is complete in 1 min or less, and, concurrently, a new absorption maximum centered at 325 nm appears. In a second reaction which requires about 1 h, the absorption spectrum of the Cu(aldimine) product slowly appears as the 325-nm band disappears. A similar 325-nm band is also observed with the Cu(II) complexes of pyridoxamine 5'-phosphate, in which the 4 position of the aromatic ring is occupied by a saturated substituent.¹⁰ Thus, it appears that this intermediate is, indeed, the carbinolamine complex, I. If too little Cu(II) is present, or if it is extensively bound as alaninate complexes, I is not observed, but PLP is converted to the aldimine complex (II) in an apparent single step reaction. Because the rate of formation of I is so much faster than its dehydration to II, the two steps may very easily be studied separately. We report here the results of a stopped flow spectrophotometric examination of the rates of formation of I as the reaction systems approached the first metastable equilibrium state. The subsequent conversion of I to II was followed using a double beam recording spectrophotometer.



Near equilibrium kinetic data provide information regarding the composition of products as well as formation rates. In this case the results of 96 determinations under a variety of conditions confirmed that I is a 1:1:1 Cu(II)-ala-PLP complex that can add one or two protons, depending on pH. The reaction conditions for a few representative experiments and their observed first-order rate constants as equilibrium was approached are given in Table I.

The data were found to conform to the rate law,

$$k_{\text{obsd}} = \left(\sum_{i=0}^4 k_{a,i} f_{\text{HiPLP}} + \sum_{i=0}^2 k_{a,i} C_u f_{\text{CuHiPLP}} \right) [\text{ala}^-] \left(1 + \frac{1}{K_{\text{cond}}} \right) \quad (2)$$

where the $k_{a,i}$ are forward rate constants for the formation of I, the f_i are the fractions of PLP present in the form of species x, and K_{cond} is the conditional equilibrium constant for carbinolamine formation. K_{cond} is equal to the ratio of the sum of the equilibrium concentrations of the unprotonated and protonated forms of I to the sum of all forms of PLP not present

Table I. Some Observed and Theoretical Values of the Near Equilibrium Rate Constants for Cu(carbinolamine) Formation ($T = 25^\circ\text{C}$, $I = 0.5$)

	$10^3 (C_{\text{U,tot}})$, M	$10^2 (A_{\text{ala,tot}})$, M	$10^4 (PLP_{\text{tot}})$, M	pH	k_{obsd} , s^{-1}	k_{calcd} , s^{-1} (no Cu terms)	k_{calcd} , s^{-1} (Cu terms)
1	5.8	5.0	1.0	5.35	0.84	0.90	0.91
2	5.8	10.0	1.0	5.14	2.2	1.7	1.7
3	1.9	2.0	1.0	6.24	3.0	3.2	3.2
4	0.49	1.0	1.0	4.20	0.22	0.17	0.18
5	5.0	1.0	5.2	6.90	0.54	0.59	0.63
6	2.0	4.4	0.8	8.83	12.8	14.5	14.6
7	4.9	1.0	1.0	4.08	0.058	0.031	0.059
8	4.9	1.0	1.0	5.11	0.082	0.044	0.076
9	5.8	0.5	1.0	5.25	0.041	0.004	0.030

Related Proceeding Appendix

none